Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 1 of 17)

This table provides information on the known or predicted interactions between INSTIs (BIC, DTG, EVG, or RAL) and non-ARV drugs. EVG is always coadministered with COBI. For information regarding interactions between INSTIs and other ARV drugs, including dosing recommendations, refer to Tables 21c, 22a, and 22b.

Recommendations for managing a particular drug interaction may differ depending on whether a new ARV drug is being initiated in a patient on a stable concomitant medication or whether a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of drug interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed concomitantly. In cases where an interacting drug needs to be replaced with an alternative, providers should exercise their clinical judgement to select the most appropriate alternative medication to use.

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Al, Mg, +/- Ca-Containing Antacids Please refer to the Miscellaneous Drugs section of this table for recommendations on use with other polyvalent cation products (e.g., Fe and Ca supplements, multivitamins).	BIC	**Al/Mg Hydroxide Antacid:** • ↔ BIC AUC if antacid is administered 2 hours after BIC and under fasting conditions • BIC AUC ↓ 52% if antacid is administered 2 hours before BIC • BIC AUC ↓ 47% to 79% if administered simultaneously with antacid **$CaCO_3$ Antacid:** • ↔ BIC AUC if administered with food • BIC AUC ↓ 33% if administered under fasting conditions	**With Antacids That Contain Al/Mg:** • Administer antacids that contain Al/Mg at least 2 hours after or 6 hours before BIC. **With Antacids That Contain Ca:** • Administer BIC and antacids that contain Ca together with food. • **Do not coadminister BIC simultaneously with antacids that contain Ca on an empty stomach.**
	DTG	DTG AUC ↓ 74% if administered simultaneously with antacid DTG AUC ↓ 26% if administered 2 hours before antacid	Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations.
	EVG/c	EVG AUC ↓ 40% to 50% if administered simultaneously with antacid EVG AUC ↓ 15% to 20% if administered 2 hours before or after antacid; ↔ with 4-hour interval	Separate EVG/c and antacid administration by more than 2 hours.
	RAL	**Al/Mg Hydroxide Antacid:** • RAL C_{min} ↓ 49% to 63% **$CaCO_3$ Antacid:** • RAL 400 mg twice daily: C_{min} ↓ 32% • RAL 1,200 mg once daily: C_{min} ↓ 48% to 57%	**Do not coadminister RAL and Al/Mg hydroxide antacids.** Use alternative acid-reducing agent. **With $CaCO_3$ Antacids:** • RAL 1,200 mg once daily: **Do not coadminister.** • RAL 400 mg twice daily: No dose adjustment or separation needed.
H2-Receptor Antagonists	BIC, DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 44% and C_{max} ↑ 60%	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 2 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers, continued			
Proton Pump Inhibitors	BIC, DTG, EVG/c	↔ INSTI	No dose adjustment needed.
	RAL	RAL AUC ↑ 37% and C_{min} ↑ 24%	No dose adjustment needed.
Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia			
Alfuzosin	BIC, DTG, RAL	↔ alfuzosin expected	No dose adjustment needed.
	EVG/c	↑ alfuzosin expected	**Contraindicated.**
Doxazosin	BIC, DTG, RAL	↔ doxazosin expected	No dose adjustment needed.
	EVG/c	↑ doxazosin possible	Initiate doxazosin at lowest dose and titrate based on doxazosin efficacy and adverse events. Doxazosin dose reduction may be needed.
Tamsulosin	BIC, DTG, RAL	↔ tamsulosin expected	No dose adjustment needed.
	EVG/c	↑ tamsulosin expected	**Do not coadminister, unless benefits outweigh risks.** If coadministered, monitor for tamsulosin-related adverse events.
Terazosin	BIC, DTG, RAL	↔ terazosin expected	No dose adjustment needed.
	EVG/c	↑ terazosin possible	Initiate terazosin at lowest dose and titrate based on terazosin efficacy and adverse events. Terazosin dose reduction may be necessary.
Silodosin	BIC, DTG, RAL	↔ silodosin expected	No dose adjustment needed.
	EVG/c	↑ silodosin expected	**Contraindicated.**
Antibacterials			
Antimycobacterials			
Rifabutin	BIC	**Rifabutin 300 mg Once Daily:** • BIC AUC ↓ 38% and C_{min} ↓ 56%	**Do not coadminister.**
	DTG	**Rifabutin 300 mg Once Daily:** • ↔ DTG AUC and C_{min} ↓ 30%	No dose adjustment needed.
	EVG/c	**Rifabutin 150 mg Every Other Day with EVG/c Once Daily Compared to Rifabutin 300 mg Once Daily Alone:** • ↔ rifabutin AUC • 25-O-desacetyl-rifabutin AUC ↑ 625% • EVG AUC ↓ 21% and C_{min} ↓ 67%	**Do not coadminister.**
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 3 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, continued			
Rifampin	BIC	BIC AUC ↓ 75%	**Contraindicated.**
	DTG	**Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Twice Daily Alone:** • DTG AUC ↓ 54% and C_{min} ↓ 72% **Rifampin with DTG 50 mg Twice Daily Compared to DTG 50 mg Once Daily Alone:** • DTG AUC ↑ 33% and C_{min} ↑ 22%	Use DTG 50 mg twice daily (instead of DTG 50 mg once daily) in patients without suspected or documented INSTI-associated resistance mutations. Consider an alternative to rifampin, such as rifabutin, in patients with certain suspected or documented INSTI-associated resistance mutations.
	EVG/c	Significant ↓ EVG and COBI expected	**Contraindicated.**
	RAL	**RAL 400 mg:** • RAL AUC ↓ 40% and C_{min} ↓ 61% **Rifampin with RAL 800 mg Twice Daily Compared to RAL 400 mg Twice Daily Alone:** • RAL AUC ↑ 27% and C_{min} ↓ 53%	Use RAL 800 mg twice daily instead of 400 mg twice daily. **Do not coadminister RAL 1,200 mg once daily with rifampin.** Monitor closely for virologic response, or consider using rifabutin as an alternative rifamycin.
Rifapentine	BIC, DTG, EVG/c	Significant ↓ BIC, DTG, EVG, and COBI expected	**Do not coadminister.**
	RAL	**Rifapentine 900 mg Once Weekly:** • RAL AUC ↑ 71% and C_{min} ↓ 12% **Rifapentine 600 mg Once Daily:** • RAL C_{min} ↓ 41%	For once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustment needed. **Do not coadminister with once-daily rifapentine.**
Macrolides			
Azithromycin	All INSTIs	↔ azithromycin expected	No dose adjustment needed.
Clarithromycin	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ clarithromycin expected	No dose adjustment needed.
	EVG/c	↑ clarithromycin expected ↑ COBI possible	Reduce clarithromycin dose by 50% in patients with CrCl 50 to 60 mL/min. **Do not coadminister in patients with CrCl <50 mL/min.** Consider alternative ARV or use azithromycin.
Erythromycin	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ erythromycin expected	No dose adjustment needed.
	EVG/c	↑ erythromycin expected ↑ COBI possible	No data available for dose recommendation. Consider alternative ARV or use azithromycin.
Anticoagulants			
Apixaban	BIC, DTG, RAL	↔ apixaban expected	No dose adjustment needed.
	EVG/c	↑ apixaban expected	**Do not coadminister** in patients who require apixaban 2.5 mg twice daily. Reduce apixaban dose by 50% in patients who require apixaban 5 mg or 10 mg twice daily.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 4 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants, continued			
Betrixaban	BIC, DTG, RAL	↔ betrixaban expected	No dose adjustment needed.
	EVG/c	↑ betrixaban expected	Administer initial single dose of betrixaban 80 mg, followed by betrixaban 40 mg once daily.
Dabigatran	BIC, DTG, RAL	↔ dabigatran expected	No dose adjustment needed.
	EVG/c	↑ dabigatran expected **With COBI 150 mg Alone:** • Dabigatran AUC ↑ 110% to 127%	Dabigatran dosing recommendation depends on indication and renal function. Refer to dabigatran prescribing information for dosing instructions when using dabigatran concomitantly with P-glycoprotein inhibitors.
Edoxaban	BIC, DTG, RAL	↔ edoxaban expected	No dose adjustment needed.
	EVG/c	↔ or ↑ edoxaban expected	**Stroke Prevention in Nonvalvular Atrial Fibrillation:** • No dose adjustment needed. **Deep Venous Thrombosis and Pulmonary Embolism:** • Administer edoxaban 30 mg once daily.
Rivaroxaban	BIC, DTG, RAL	↔ rivaroxaban expected	No dose adjustment needed.
	EVG/c	↑ rivaroxaban expected	**Do not coadminister.**
Warfarin	BIC, DTG, RAL	↔ warfarin expected	No dose adjustment needed.
	EVG/c	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	BIC	↓ BIC possible	**Do not coadminister.**
	DTG	DTG AUC ↓ 49%	Increase DTG dose to 50 mg twice daily in ART-naive or ART-experienced, INSTI-naive patients. **Do not coadminister in INSTI-experienced patients with known or suspected INSTI resistance.**
	EVG/c	Carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Do not coadminister.**
Eslicarbazepine	All INSTIs	↓ INSTI possible ↓ COBI possible	Consider alternative ARV or anticonvulsant.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 5 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants, continued			
Ethosuximide	BIC, DTG, RAL	↔ ethosuximide expected	No dose adjustment needed.
	EVG/c	↑ ethosuximide possible	Monitor for ethosuximide-related adverse events.
Lamotrigine	BIC, DTG, RAL	↔ lamotrigine expected	No dose adjustment needed.
	EVG/c	No data	Monitor anticonvulsant concentrations and adjust dose accordingly.
Oxcarbazepine	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c, RAL	↓ EVG/c and RAL possible	Consider alternative ARV or anticonvulsant.
Phenobarbital Phenytoin	BIC	↓ BIC possible	**Do not coadminister.**
	DTG	↓ DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG/c expected	**Contraindicated.**
	RAL	↓ or ↔ RAL possible	**Do not coadminister.**
Valproic Acid	All INSTIs	No data	Monitor valproic acid concentration and virologic response.
Antidepressants, Anxiolytics, Antipsychotics Also see Sedative/Hypnotics section below			
Aripiprazole	BIC, DTG, RAL	↔ aripiprazole expected	No dose adjustment needed.
	EVG/c	↑ aripiprazole expected	Administer 25% of the usual aripiprazole dose. Titrate based on aripiprazole efficacy and adverse events. Refer to aripiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Brexpiprazole	BIC, DTG, RAL	↔ brexpiprazole expected	No dose adjustment needed.
	EVG/c	↑ brexpiprazole expected	Administer 25% of the usual brexpiprazole dose. Titrate based on brexpiprazole efficacy and adverse events. Refer to brexpiprazole label for dosing recommendations in patients who are known to be CYP2D6 poor metabolizers or who have major depressive disorder.
Bupropion	BIC, DTG, RAL	↔ bupropion expected	No dose adjustment needed.
	EVG/c	↑ bupropion possible	Titrate bupropion dose based on clinical response.
Buspirone	BIC, DTG, RAL	↔ buspirone expected	No dose adjustment needed.
	EVG/c	↑ buspirone possible	Initiate buspirone at a low dose. Buspirone dose reduction may be needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 6 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, Antipsychotics, continued Also see Sedative/Hypnotics section below			
Cariprazine	BIC, DTG, RAL	↔ cariprazine expected	No dose adjustment needed.
	EVG/c	↑ cariprazine expected	**Starting Cariprazine in a Patient Who Is Already Receiving EVG/c:** • Administer cariprazine 1.5 mg on Day 1 and Day 3, with no dose given on Day 2. From Day 4 onward, administer cariprazine 1.5 mg daily. Dose can be increased to a maximum dose of 3 mg daily. If EVG/c is withdrawn, cariprazine dose may need to be increased. **Starting EVG/c in a Patient Who is Already Receiving Cariprazine:** • For patients receiving cariprazine 3 mg or 6 mg daily, reduce cariprazine dose by half. For patients taking cariprazine 4.5 mg daily, the dose should be reduced to 1.5 mg or 3 mg daily. For patients taking cariprazine 1.5 mg daily, change to 1.5 mg every other day. If EVG/c is withdrawn, cariprazine dose may need to be increased.
Iloperidone	BIC, DTG, RAL	↔ iloperidone expected	No dose adjustment needed.
	EVG/c	↑ iloperidone expected	Decrease iloperidone dose by 50%.
Lurasidone	BIC, DTG, RAL	↔ lurasidone expected	No dose adjustment needed.
	EVG/c	↑ lurasidone expected	**Contraindicated.**
Nefazodone	BIC, DTG, RAL	↔ nefazodone expected	No dose adjustment needed.
	EVG/c	↑ nefazodone expected	Consider alternative ARV or antidepressant.
Pimavanserin	BIC, DTG, RAL	↔ pimavanserin expected	No dose adjustment needed.
	EVG/c	↑ pimavanserin expected	Reduce pimavanserin dose to 10 mg.
Pimozide	BIC, DTG, RAL	↔ pimozide expected	No dose adjustment needed.
	EVG/c	↑ pimozide expected	**Contraindicated.**
Quetiapine	BIC, DTG, RAL	↔ quetiapine expected	No dose adjustment needed.
	EVG/c	↑ quetiapine AUC expected	**Starting Quetiapine in a Patient Receiving EVG/c:** • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine efficacy and adverse events. **Starting EVG/c in a Patient Receiving a Stable Dose of Quetiapine:** • Reduce quetiapine dose to 1/6 of the current dose, and closely monitor for quetiapine efficacy and adverse events.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 7 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antidepressants, Anxiolytics, Antipsychotics, continued Also see Sedative/Hypnotics section below			
Selective Serotonin Reuptake Inhibitors Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	EVG/c	↔ EVG ↔ sertraline	No dose adjustment needed.
		↑ other SSRIs possible	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response.
	BIC, DTG, RAL	↔ BIC, DTG and RAL expected ↔ SSRI expected	No dose adjustment needed.
Tricyclic Antidepressants Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	BIC, DTG, RAL	↔ TCA expected	No dose adjustment needed.
	EVG/c	Desipramine AUC ↑ 65%	Initiate with lowest dose of TCA and titrate dose carefully.
		↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug concentrations.
Trazodone	BIC, DTG, RAL	↔ trazodone expected	No dose adjustment needed.
	EVG/c	↑ trazodone possible	Initiate with lowest dose of trazodone and titrate dose carefully.
Ziprasidone	BIC, DTG, RAL	↔ ziprasidone expected	No dose adjustment needed.
	EVG/c	↑ ziprasidone possible	Monitor for ziprasidone-related adverse events.
Other Antipsychotics CYP3A4 and/or CYP2D6 substrates (e.g., perphenazine, risperidone, thioridazine)	EVG/c	↑ antipsychotic possible	Initiate antipsychotic at a low dose. Antipsychotic dose reduction may be needed.
Antifungals			
Isavuconazole	BIC	↑ BIC possible	No dose adjustment needed.
	EVG/c	↑ isavuconazole expected ↑ or ↓ EVG and COBI possible	If coadministered, consider monitoring isavuconazole concentrations and assessing virologic response.
Itraconazole	BIC	↑ BIC expected	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ itraconazole expected	No dose adjustment needed.
	EVG/c	↑ itraconazole expected ↑ EVG and COBI possible	Consider monitoring itraconazole concentrations to guide dose adjustments. **Do not coadminister with high itraconazole doses (>200 mg/day) unless guided by itraconazole concentrations.**

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 8 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals, continued			
Posaconazole	BIC	↑ BIC expected	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ posaconazole expected	No dose adjustment needed.
	EVG/c	↑ EVG and COBI possible ↑ posaconazole possible	If coadministered, monitor posaconazole concentrations.
Voriconazole	BIC	↑ BIC possible	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ voriconazole expected	No dose adjustment needed.
	EVG/c	↑ voriconazole expected ↑ EVG and COBI possible	**Do not coadminister voriconazole and COBI unless benefit outweighs risk.** If coadministered, consider monitoring voriconazole concentrations and adjust dose accordingly.
Antihyperglycemics			
Metformin	BIC	Metformin AUC ↑ 39%	Monitor for adverse events of metformin.
	DTG	**DTG 50 mg Once Daily plus Metformin 500 mg Twice Daily:** • Metformin AUC ↑ 79% and C_{max} ↑ 66% **DTG 50 mg Twice Daily plus Metformin 500 mg Twice Daily:** • Metformin AUC ↑ 2.4-fold and C_{max} ↑ 2-fold	Start metformin at lowest dose and titrate based on glycemic control. Monitor for adverse events of metformin. When starting/stopping DTG in patients on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize adverse events of metformin.
	RAL	↔ metformin expected	No dose adjustment needed.
Saxagliptin	BIC, DTG, RAL	↔ saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	Limit saxagliptin dose to 2.5 mg once daily.
Dapagliflozin/Saxagliptin	BIC, DTG, RAL	↔ dapagliflozin or saxagliptin expected	No dose adjustment needed.
	EVG/c	↑ saxagliptin expected	**Do not coadminister.** Dapagliflozin is only available as a coformulated drug that contains 5 mg of saxagliptin. When coadministered with EVG/c, the dose of saxagliptin should not exceed 2.5 mg once daily; thus, this combination **is not recommended**.
Antiplatelets			
Clopidogrel	BIC, DTG, RAL	↔ clopidogrel expected	No dose adjustment needed.
	EVG/c	↓ clopidogrel active metabolite, with impaired platelet inhibition expected	**Do not coadminister.**
Prasugrel	BIC, DTG, RAL	↔ prasugrel expected	No dose adjustment needed.
	EVG/c	↓ prasugrel active metabolite, with no impairment of platelet inhibition expected	Insufficient data to make a dose recommendation.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 9 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antiplatelets, continued			
Ticagrelor	BIC, DTG, RAL	↔ ticagrelor expected	No dose adjustment needed.
	EVG/c	↑ ticagrelor expected	**Do not coadminister.**
Vorapaxar	BIC, DTG, RAL	↔ vorapaxar expected	No dose adjustment needed.
	EVG/c	↑ vorapaxar expected	**Do not coadminister.**
Beta-Agonists, Long-Acting Inhaled			
Arformoterol, Formoterol	All INSTIs	↔ arformoterol or formoterol expected	No dose adjustment needed.
Indacaterol	BIC, DTG, RAL	↔ indacaterol expected	No dose adjustment needed.
	EVG/c	↑ indacaterol expected	
Olodaterol	BIC, DTG, RAL	↔ olodaterol expected	No dose adjustment needed.
	EVG/c	↑ olodaterol expected	
Salmeterol	BIC, DTG, RAL	↔ salmeterol expected	No dose adjustment needed.
	EVG/c	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events.
Cardiac Medications			
Amiodarone	BIC, DTG, RAL	↔ INSTI expected ↔ amiodarone expected	No dose adjustment needed.
	EVG/c	↑ INSTI possible ↑ amiodarone possible	**Do not coadminister, unless benefits outweigh risks.** If coadministration is necessary, monitor for amiodarone-related adverse events and consider monitoring ECG and amiodarone concentrations.
Bepridil, Digoxin, Disopyramide, Dronedarone, Flecainide, Systemic Lidocaine, Mexilitine, Propafenone, Quinidine	BIC, DTG	↔ expected for the listed antiarrhythmics, except for disopyramide ↑ disopyramide possible	No dose adjustment needed. Monitor for disopyramide-related adverse events.
	RAL	↔ expected for the listed antiarrhythmics	No dose adjustment needed.
	EVG/c	↑ antiarrhythmics possible Digoxin C_{max} ↑ 41% and ↔ AUC	Therapeutic drug monitoring for antiarrhythmics, if available, is recommended.
Beta-Blockers (e.g., metoprolol, timolol)	BIC, DTG, RAL	↔ beta-blocker expected	No dose adjustment needed.
	EVG/c	↑ beta-blocker possible	Beta-blocker dose may need to be decreased; adjust dose based on clinical response. Consider using an alternative ARV, or a beta-blocker that is not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol).

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 10 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Cardiac Medications, continued			
Bosentan	BIC, DTG	↓ BIC and DTG possible	No dose adjustment needed.
	RAL	↔ bosentan expected	No dose adjustment needed.
	EVG/c	↑ bosentan possible	**In Patients on EVG/c ≥10 Days:** • Start bosentan at 62.5 mg once daily or every other day based on individual tolerability. **In Patients on Bosentan Who Require EVG/c:** • Stop bosentan ≥36 hours before EVG/c initiation. At least 10 days after initiation of EVG/c, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability.
Calcium Channel Blockers	BIC	↑ BIC possible with diltiazem ↔ expected for all other CCBs	No dose adjustment needed.
	DTG, RAL	↔ INSTI expected ↔ CCB expected	No dose adjustment needed.
	EVG/c	↑ CCB possible	Titrate CCB dose and monitor for CCB efficacy and adverse events.
Dofetilide	BIC, DTG	↑ dofetilide expected	**Contraindicated.**
	RAL	↔ dofetilide expected	No dose adjustment needed.
	EVG/c	↑ dofetilide possible	**Do not coadminister.**
Eplerenone	BIC, DTG, RAL	↔ eplerenone expected	No dose adjustment needed.
	EVG/c	↑ eplerenone expected	**Contraindicated.**
Ivabradine	BIC, DTG, RAL	↔ ivabradine expected	No dose adjustment needed.
	EVG/c	↑ ivabradine expected	**Contraindicated.**
Ranolazine	BIC, DTG, RAL	↔ ranolazine expected	No dose adjustment needed.
	EVG/c	↑ ranolazine expected	**Contraindicated.**
Corticosteroids			
Beclomethasone Inhaled or intranasal	BIC, DTG, EVG/c, RAL	↔ glucocorticoid expected	No dose adjustment needed.
Budesonide, Ciclesonide, Fluticasone, Mometasone Inhaled or intranasal	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid possible	**Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Coadministration can result in adrenal insufficiency and Cushing's syndrome. Consider using an alternative corticosteroid (e.g., beclomethasone).

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 11 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Corticosteroids, continued			
Betamethasone, Budesonide Systemic	BIC, DTG, RAL	↔ INSTI expected ↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoids possible ↓ EVG possible	**Do not coadminister unless potential benefits of systemic budesonide outweigh the risks of systemic corticosteroid adverse effects.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.
Dexamethasone Systemic	BIC	↓ BIC possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
	DTG, RAL	↔ INSTI expected	No dose adjustment needed.
	EVG/c	↓ EVG and COBI possible	Consider alternative corticosteroid for long-term use or alternative ARV. If coadministration is necessary, monitor virologic response to ART.
Prednisone, Prednisolone Systemic	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ prednisolone possible	Coadministration may be considered if the potential benefits outweigh the risks of systemic corticosteroid adverse effects. If coadministration is necessary, monitor for adrenal insufficiency and Cushing's syndrome.
Betamethasone, Methylprednisolone, Prednisolone, Triamcinolone Local injections, including intra-articular, epidural, or intra-orbital	BIC, DTG, RAL	↔ glucocorticoid expected	No dose adjustment needed.
	EVG/c	↑ glucocorticoid expected	**Do not coadminister.** Coadministration may result in adrenal insufficiency and Cushing's syndrome.
Hepatitis C Direct-Acting Antiviral Agents			
Daclatasvir	BIC, RAL	No data	No dose adjustment needed.
	DTG	↔ daclatasvir	No dose adjustment needed.
	EVG/c	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Dasabuvir plus Ombitasvir/Paritaprevir/RTV	BIC, DTG	No data	No dose adjustment needed.
	EVG/c	No data	**Do not coadminister.**
	RAL	RAL AUC ↑ 134%	No dose adjustment needed.
Elbasvir/Grazoprevir	BIC	↔ BIC expected	No dose adjustment needed.
	DTG	↔ elbasvir ↔ grazoprevir ↔ DTG	No dose adjustment needed.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 12 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hepatitis C Direct-Acting Antiviral Agents, continued			
Elbasvir/Grazoprevir	EVG/c	↑ elbasvir expected ↑ grazoprevir expected	**Do not coadminister.**
	RAL	↔ elbasvir ↔ grazoprevir ↔ RAL with elbasvir RAL AUC ↑ 43% with grazoprevir	No dose adjustment needed.
Glecaprevir/Pibrentasvir	BIC	↔ BIC expected	No dose adjustment needed.
	DTG, RAL	No significant effect	No dose adjustment needed.
	EVG/c	Glecaprevir AUC ↑ 3-fold Pibrentasvir AUC ↑ 57% EVG AUC ↑ 47%	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
Ledipasvir/Sofosbuvir	BIC, DTG, RAL	↔ DTG and RAL	No dose adjustment needed.
	EVG/c/ TDF/FTC	↑ TDF expected ↑ ledipasvir expected	**Do not coadminister.**
	EVG/c/ TAF/FTC	↔ EVG/c/TAF/FTC expected	No dose adjustment needed.
Sofosbuvir	All INSTIs	↔ INSTI expected ↔ sofosbuvir expected	No dose adjustment needed.
Sofosbuvir/Velpatasvir	All INSTIs	↔ INSTI expected ↔ sofosbuvir and velpatasvir expected	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events.
Sofosbuvir/Velpatasvir/ Voxilaprevir	EVG/c	**When Administered with Sofosbuvir/ Velpatasvir/Voxilaprevir (400 mg/100 mg/100 mg) plus Voxilaprevir 100 mg:** • Sofosbuvir AUC ↑ 22% • ↔ velpatasvir • Voxilaprevir AUC ↑ 2-fold	No dose adjustment needed. If coadministered with TDF, monitor for TDF-related adverse events. Consider monitoring for hepatotoxicity if coadministered with TDF or TAF.
	BIC, DTG, RAL	↔ INSTI expected ↔ sofosbuvir, velpatasvir, and voxilaprevir expected	No dose adjustment needed.
Herbal Products			
St. John's Wort	BIC, DTG	↓ BIC and DTG possible	**Do not coadminister.**
	EVG/c	↓ EVG and COBI expected	**Contraindicated.**
Hormonal Therapies			
Contraceptives: Non-Oral	All INSTIs	No data	No drug-drug interaction studies have been conducted with INSTIs and non-oral routes of hormone administration. It is unclear whether drug-drug interaction data for oral drugs can be used to predict interactions for non-oral drugs.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 13 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Therapies, continued			
Contraceptives – Oral	BIC, DTG, RAL	↔ ethinyl estradiol and norgestimate ↔ INSTI	No dose adjustment needed.
	EVG/c	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and C_{min} ↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and may include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of using the drug and consider using an alternative ARV or contraceptive method.
		↑ drospirenone possible	Clinical monitoring is recommended, due to the potential for hyperkalemia. Consider using alternative ARV or contraceptive method.
Gender-Affirming Therapy	BIC, DTG, EVG/c, RAL	↔ goserelin, leuprolide acetate, and spironolactone expected	No dose adjustment needed.
	BIC, DTG, RAL	↔ estrogen expected	No dose adjustment needed.
		↔ testosterone expected	No dose adjustment needed.
	EVG/c	↓ or ↑ estradiol possible ↑ dutasteride and finasteride possible	Adjust dutasteride dose as needed based on clinical effects and endogenous hormone concentrations.
		↑ testosterone possible	Monitor masculinizing effects of testosterone and monitor for adverse effects. Adjust testosterone dose as necessary.
Menopausal Replacement Therapy	BIC, DTG, RAL	↔ estrogen expected with estradiol or conjugated estrogen (equine and synthetic) ↔ drospirenone, medroxyprogesterone, and micronized progesterone expected	No dose adjustment needed.
	EVG/c	↓ or ↑ estrogen possible ↑ drospirenone possible ↑ oral medroxyprogesterone possible ↑ oral micronized progesterone possible	Adjust estrogen and progestin dose as needed based on clinical effects.
Immunosuppressants			
Cyclosporine, Everolimus, Sirolimus, Tacrolimus	BIC, DTG, RAL	↔ immunosuppressant expected	No dose adjustment needed.
	EVG/c	↑ immunosuppressant possible	Initiate with an adjusted dose of immunosuppressant to account for potential increased concentrations of the immunosuppressant and monitor for immunosuppressant-related adverse events. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with a specialist as necessary.
Lipid-Modifying Agents			
Atorvastatin	BIC, DTG, RAL	↔ atorvastatin expected	No dose adjustment needed.
	EVG/c	Atorvastatin AUC ↑ 2.6-fold and C_{max} ↑ 2.3-fold	Titrate statin dose carefully and administer the lowest effective dose while monitoring for adverse events. Do not exceed 20 mg atorvastatin daily.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 14 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lipid-Modifying Agents, continued			
Lomitapide	BIC, DTG, RAL	↔ lomitapide expected	No dose adjustment needed.
	EVG/c	↑ lomitapide expected	**Contraindicated.**
Lovastatin	BIC, DTG, RAL	↔ lovastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ lovastatin expected	**Contraindicated.**
Pitavastatin, Pravastatin	BIC, DTG, RAL	↔ statin expected	No dose adjustment needed.
	EVG/c	No data	No data available for dose recommendation.
Rosuvastatin	BIC, DTG, RAL	↔ rosuvastatin expected	No dose adjustment needed.
	EVG/c	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose carefully and use the lowest effective dose while monitoring for adverse events.
Simvastatin	BIC, DTG, RAL	↔ simvastatin expected	No dose adjustment needed.
	EVG/c	Significant ↑ simvastatin expected	**Contraindicated.**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine Sublingual, buccal, or implant	BIC, DTG	↔ buprenorphine and norbuprenorphine (active metabolite) expected	No dose adjustment needed.
	EVG/c	Buprenorphine AUC ↑ 35% and C_{min} ↑ 66% Norbuprenorphine (active metabolite) AUC ↑ 42% and C_{min} ↑ 57%	No dose adjustment needed. Monitor for adverse events of buprenorphine. When transferring buprenorphine from transmucosal administration to implantation, monitor to ensure buprenorphine effect is adequate and not excessive.
	RAL	↔ buprenorphine and norbuprenorphine (active metabolite) (sublingual) ↔ buprenorphine or norbuprenorphine (active metabolite) expected (implant)	No dose adjustment needed.
Fentanyl	BIC, DTG, RAL	↔ fentanyl expected	No dose adjustment needed.
	EVG/c	↑ fentanyl	Monitor for fentanyl efficacy and adverse events, including potentially fatal respiratory depression.
Lofexidine	BIC, DTG, RAL	↔ lofexidine expected	No dose adjustment needed.
	EVG/c	↑ lofexidine possible	Monitor for lofexidine-related adverse events, including symptoms of orthostasis and bradycardia.
Methadone	All INSTIs	↔ methadone	No dose adjustment needed.
Tramadol	BIC, DTG, RAL	↔ tramadol and M1 (active metabolite) expected	No dose adjustment needed.
	EVG/c	↑ tramadol expected ↓ M1 (active metabolite) possible	Tramadol dose adjustments may be necessary. Monitor for clinical response and tramadol-related adverse events.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 15 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PDE5 Inhibitors			
Avanafil	BIC, DTG, RAL	↔ avanafil expected	No dose adjustment needed.
	EVG/c	No data	**Do not coadminister.**
Sildenafil	BIC, DTG, RAL	↔ sildenafil expected	No dose adjustment needed.
	EVG/c	↑ sildenafil expected	**For Treatment of Erectile Dysfunction:** • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. **Contraindicated** for treatment of PAH.
Tadalafil	BIC, DTG, RAL	↔ tadalafil expected	No dose adjustment needed.
	EVG/c	↑ tadalafil expected	**For Treatment of Erectile Dysfunction:** • Start with tadalafil 5 mg and do not exceed a single dose of tadalafil 10 mg every 72 hours. Monitor for adverse effects of tadalafil. **For Treatment of PAH** *In Patients on EVG/c >7 Days:* • Start with tadalafil 20 mg once daily and increase to tadalafil 40 mg once daily based on tolerability. *In Patients on Tadalafil who Require EVG/c:* • Stop tadalafil ≥24 hours before EVG/c initiation. Seven days after EVG/c initiation, restart tadalafil at 20 mg once daily, and increase to tadalafil 40 mg once daily based on tolerability.
Vardenafil	BIC, DTG, RAL	↔ vardenafil expected	No dose adjustment needed.
	EVG/c	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Buspirone	BIC, DTG, RAL	↔ buspirone expected	No dose adjustment needed.
	EVG/c	↑ buspirone expected	Initiate buspirone at a low dose. Dose reduction may be needed.
Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam	BIC, DTG, RAL	↔ benzodiazepine expected	No dose adjustment needed.
	EVG/c	↑ benzodiazepine possible	Dose reduction of benzodiazepine may be necessary. Initiate with a low dose and monitor for benzodiazepine-related adverse events. Consider using an alternative benzodiazepine, such as lorazepam, oxazepam, or temazepam.
Midazolam, Triazolam	BIC, RAL	↔ benzodiazepine expected	No dose adjustment needed.

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Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Sedative/Hypnotics, continued			
Midazolam, Triazolam, continued	DTG	**With DTG 25 mg:** • ↔ midazolam AUC	No dose adjustment needed.
	EVG/c	↑ midazolam expected ↑ triazolam expected	**Contraindicated. Do not coadminister triazolam or oral midazolam and EVG/c.** Parenteral midazolam can be administered in a closely monitored setting. Consider dose reduction, especially if >1 dose is administered.
Suvorexant	BIC, DTG, RAL	↔ suvorexant expected	No dose adjustment needed.
	EVG/c	↑ suvorexant expected	**Do not coadminister.**
Zolpidem	BIC, DTG, RAL	↔ zolpidem expected	No dose adjustment needed.
	EVG/c	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction of zolpidem may be necessary.
Miscellaneous Drugs			
Calcifediol	BIC, DTG, RAL	↔ calcifediol expected	No dose adjustment needed.
	EVG/c	↑ calcifediol possible	Dose adjustment of calcifediol may be required. Monitor serum 25-hydroxyvitamin D, intact PTH, and serum Ca concentrations.
Cisapride	BIC, DTG, RAL	↔ cisapride expected	No dose adjustment needed.
	EVG/c	↑ cisapride expected	**Contraindicated.**
Colchicine	BIC, DTG, RAL	↔ colchicine expected	No dose adjustment needed.
	EVG/c	↑ colchicine expected	**Do not coadminister in patients with hepatic or renal impairment.** **For Treatment of Gout Flares:** • Administer a single dose of colchicine 0.6 mg, followed by colchicine 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. **For Prophylaxis of Gout Flares:** • If original dose was colchicine 0.6 mg twice daily, decrease to colchicine 0.3 mg once daily. If dose was 0.6 mg once daily, decrease to 0.3 mg every other day. **For Treatment of Familial Mediterranean Fever:** • Do not exceed colchicine 0.6 mg once daily or 0.3 mg twice daily.
Dronabinol	BIC, DTG, RAL	↔ dronabinol expected	No dose adjustment needed.
	EVG/c	↑ dronabinol possible	Monitor for dronabinol-related adverse events.

Table 21d. Drug Interactions Between Integrase Strand Transfer Inhibitors and Other Drugs (Last updated December 18, 2019; last reviewed December 18, 2019) (page 17 of 17)

Concomitant Drug	INSTI	Effect on INSTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Drugs, continued			
Eluxadoline	BIC, DTG, RAL	↔ eluxadoline expected	No dose adjustment needed.
	EVG/c	↑ eluxadoline possible	Monitor for eluxadoline-related adverse events.
Ergot Derivatives	BIC, DTG, RAL	↔ dihydroergotamine, ergotamine, and methylergonovine expected	No dose adjustment needed.
	EVG/c	↑ dihydroergotamine, ergotamine, and methylergonovine expected	**Contraindicated.**
Flibanserin	BIC, DTG, RAL	↔ flibanserin expected	No dose adjustment needed.
	EVG/c	↑ flibanserin expected	**Contraindicated.**
Polyvalent Cation Supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals **Note:** Please refer to the Acid Reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids.	BIC	↔ BIC AUC if administered simultaneously with Fe or Ca and food BIC AUC ↓ 33% if administered simultaneously with $CaCO_3$ under fasting conditions BIC AUC ↓ 63% if administered simultaneously with Fe under fasting conditions	**With Supplements That Contain Ca or Fe:** • Administer BIC and supplements that contain Ca or Fe together with food. **Do not coadminister BIC under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.**
	DTG	DTG AUC ↓ 39% if administered simultaneously with $CaCO_3$ under fasting conditions DTG AUC ↓ 54% if administered simultaneously with Fe under fasting conditions ↔ DTG when administered with Ca or Fe supplement simultaneously with food	**With Supplements That Contain Ca or Fe:** • Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement. **Do not coadminister DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe.**
	EVG/c, RAL	↓ INSTI possible	If coadministration is necessary, administer INSTI at least 2 hours before or at least 6 hours after supplements that contain polyvalent cations, including but not limited to the following products: cation-containing laxatives; Fe, Ca, or Mg supplements; and sucralfate. Monitor for virologic response. Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; AUC = area under the curve; BIC = bictegravir; Ca = calcium; $CaCO_3$ = calcium carbonate; CCB = calcium channel blocker; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P; DAA = direct-acting antiviral; DTG = dolutegravir; ECG = electrocardiogram; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; HCV = hepatitis C virus; INR= international normalized ratio; INSTI = integrase strand transfer inhibitor; Mg = magnesium; PAH = pulmonary arterial hypertension; PDE5 = Phosphodiesterase Type 5; PTH = parathyroid hormone; RAL = raltegravir; RTV = ritonavir; SSRI = selective serotonin reuptake inhibitors; TAF = tenofovir alafenamide; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; Zn = zinc